



Attorney Docket 1662/63303

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : Igor RUKHMAN et al.  
 Serial No. : 10/802,627  
 Filed : March 17, 2004  
 Title : POLYMORPHS OF VALSARTAN  
 Examiner : Chung, Susannah Lee  
 Art Unit : 1626

## Declaration of Dr. Tamás Koltai Under 37 CFR 1.132

I, Dr. Tamás Koltai, do hereby declare as follows:

1. I am employed at Teva Pharmaceutical Industries in Petah Tiqva, Israel, as a Senior Researcher, Physical R&D. I have a Ph.D. in Environmental Chemistry from the University of Veszprém, Hungary. I have substantial industrial experience working with polymorphism in pharmaceutical substances. I am an inventor on the patent application currently under review, US Ser. No. 10/802,627 ('627).
2. I have reviewed U.S. Patent No. 5,399,578 to Buhlmayer et al. ('578).
3. The '578 patent prepares valsartan in examples 16 and 37.
4. The '578 patent fails to state whether the product of examples 16 and 37 is crystalline or amorphous.
5. The melting point provided for the valsartan of Example 37 is 116-117°C.
6. In my opinion, the product of Example 37 is a crystalline material because an amorphous product would not have a sharp melting point where there is a slight difference between the lower and higher number of the melting point range.
7. The melting range provided for the product of Example 16 is 105-115°C.
8. My colleague, Dr. Valerie Niddam-Hildesheim, had informed me that two crystallization experiments of valsartan from ethyl acetate, as was described in the Buhlmayer patent, were carried out under her supervision.. These are designated samples A and B. Dr. Niddam-Hildesheim's procedure is described in an accompanying declaration.
- ~~9. The samples were analyzed by powder XRD with a Scintag X-Ray powder diffractometer model X'TRA, Cu-tube, solid state detector. The sample holder was a round standard aluminum sample holder with round zero background quartz plate with cavity of 25 (diameter)\*0.5 (dept.) mm. The scanning parameters were regular scan: Range: 2-40 or 2-30 deg.2θ: continuous scan, Rate: 3.00 or 5.00 deg./min.~~
10. The following two XRD patterns were obtained for the samples.

Fig. 1 - X-Ray Diffraction (XRD) pattern of sample A

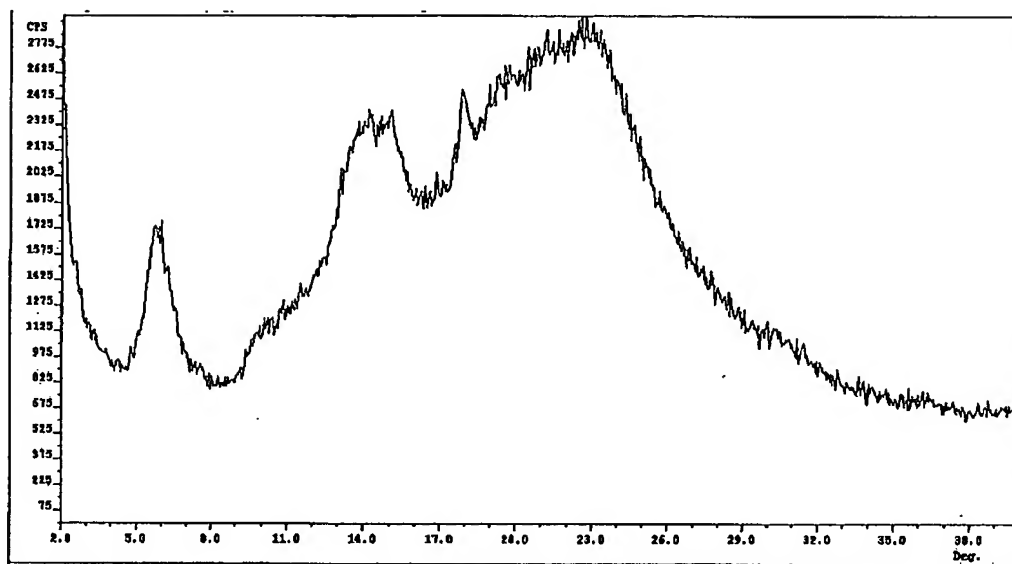
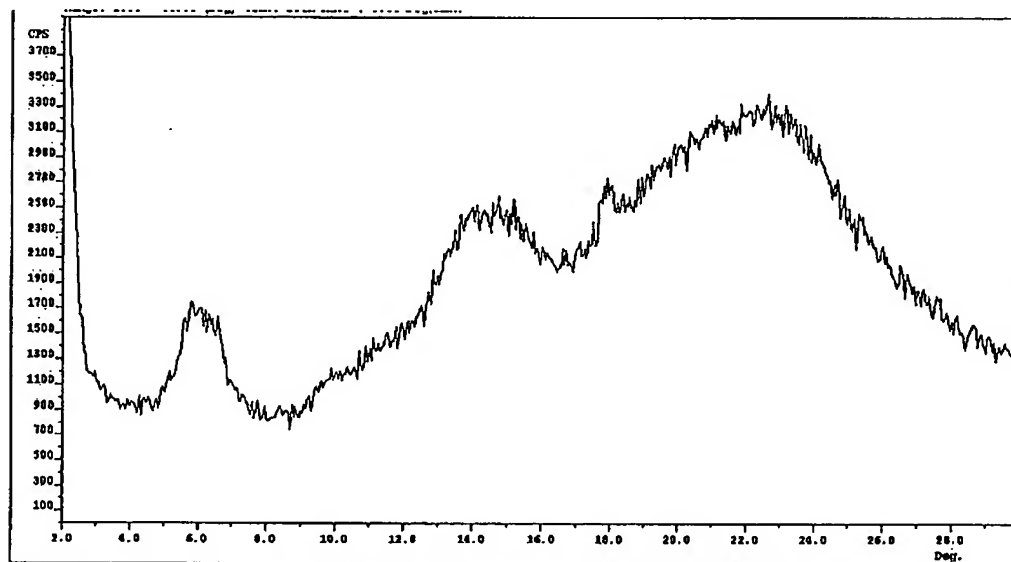


Fig. 2 - X-Ray Diffraction (XRD) pattern of sample B.



11. In my opinion the XRD patterns of both samples are essentially identical. The XRD patterns show that the samples are amorphous but contain a substantial amount of crystalline material as apparent from the peaks present in the XRD pattern. A highly amorphous valsartan product would consist of a single halo pattern without peaks. For an example of an XRD pattern of pure amorphous valsartan, showing such a pattern, see Figure 2 of the '627 patent application.

12. I have reviewed WO 02/06253 (WO '253), which lists Bulmayer as an inventor. WO '253 describes valsartan, presumably obtained by the methods in the Buhlmayer '578 patent, as "almost amorphous" under X-ray analysis (presumably XRD).<sup>1</sup> WO '253, page 2, line 2. However, WO '253 does not show the XRD diffractogram of the "almost amorphous" valsartan. WO '253 further states that free acid valsartan has a measured melting enthalpy of 12 kJ/mol (approximately 28 J/g).<sup>2</sup> In my opinion, this high enthalpy confirms the "existence of a considerable residual arrangement in the particles or structural domains for the free acid valsartan." WO '253, page 2, lines 3-5.
13. I have been advised by counsel that the broadest product claim pending in the Office Action under review is as follows:
17. Amorphous form of valsartan, wherein the amorphous form has a DSC thermogram that lacks a melting enthalpy above about 1 J/g.
14. In my opinion, the product recited in this claim is substantially different than the product obtained from crystallization from ethyl acetate, as disclosed by Buhlmayer in the '578 patent.
15. An enthalpy of about 1 J/g is very low and the product has to be highly amorphous to exhibit such a low enthalpy in DSC. If crystalline material is present, the melting of the crystalline material would have an enthalpy of much higher than about 1 J/g.
16. In my opinion, the samples of valsartan obtained from ethyl acetate by Dr. Niddam-Hildesheim, using the method of Buhlmayer, shows amorphous valsartan contaminated by crystalline valsartan. This contamination explains the report in WO '253 of a melting enthalpy of 12 kJ/mol. Therefore, it is my opinion that the Buhlmayer '578 patent fails to teach a process for preparation of pure amorphous valsartan with an enthalpy of no more than about 1 J/g.

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<sup>1</sup> Counsel has informed me that the '578 patent is the US counterpart to EP 0443983, cited in the '253 specification.

<sup>2</sup> Valsartan has a mass of 435g/mole. 12000J/mole divided by 435g/mole is about 28 J/g.

17. The undersigned declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the life so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and this such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Tamás Koltai

Tamás Koltai, Ph.D.  
Senior Researcher, Physical R&D  
Teva Pharmaceutical Industries, Israel

22/7/08  
Date



## **Curriculum Vitae**

Name: Tamás KOLTAI  
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### **Education**

1995-1998: Ph.D. in Environmental Chemistry. University of Veszprém, Hungary.  
1993-1995: M.Sc. in Chemical engineering. University of Veszprém, Hungary.  
1990-1993: B.Sc. University of Veszprém, Hungary Department of Analytical Chemistry.

### **Professional Experience**

2008-- Senior researcher: Teva Pharmaceutical industries Ltd. Assia, Petach Tiqua, Physical R&D. Research to obtain novel crystalline and amorphous forms of pharmaceutical compounds. Support of process development and searching new techniques to increase the yield and efficiency of the processes.

2003-2008: Project coordinator: Teva Pharmaceutical industries Ltd. Assia, Petach Tiqua, Physical R&D. Research to obtain and characterize novel crystalline and amorphous forms of pharmaceutical compounds.

2001-2003: Project fellow. Agricultural Research Organization (ARO), Department of Postharvest Science of Fresh Produce, Bet Dagan, Israel. Microbiocidal formulation comprising an essential oil or their derivatives

1999-2000: Project fellow (Post doctoral status). Research Institute of Catalysis of the CNRS (National Research Center of Sciences), Villeurbanne, France. Evaluation of a new procedure of desulfuration of oil fractions.

1995-2000: Project fellow. Institute of Isotopes of the Hungarian Academy of Sciences, Budapest, Hungary. Study of Hydrodesulfuration catalysts with isotopic method.

### **Publications**

Fourteen journal articles on sulfur chemistry

Named as inventor on 38 patent applications with Teva Pharmaceuticals, all pertaining to polymorphic studies of pharmaceutical substances; includes five US granted patents and one Japanese granted patent.



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Art Unit : 1626

**Declaration of Valerie Niddam-Hildesheim, Ph.D. Under 37 CFR 1.132**

I, Valerie Niddam-Hildesheim, Ph.D., do hereby declare:

1. I am employed by Teva Pharmaceutical Industries, Ltd., in Petah Tiqva, Israel, as a Project Manager in Process Development Chemistry. I have a Ph.D. in organic chemistry from the University of Aix-Marseille II, France. I have substantial experience in the organic synthesis and process development of pharmaceutical compounds. I am familiar with the preparation of valsartan as discussed in this case.

2. I have reviewed U.S. Patent No. 5,399,578 to Buhlmayer et al.

3. The '578 patent prepares valsartan in example 16.

4. The relevant portion of Example 16 states:

The product can be prepared starting from 1.40 g of N-valeryl-N-[(2'-cyanobiphenyl-4-yl)methyl]-(L)-valine methyl ester and 2.25 g of tributyltin azide with subsequent flash chromatography (B1). FAB-MS (M+H).sup.+ =436, melting interval 105°-115° (from ethyl acetate).

5. As apparent, Example 16 does not provide a detailed crystallization process other than stating "from ethyl acetate."

6. Two crystallization experiments of valsartan from ethyl acetate were carried out under my supervision. Attached are true and accurate copies of laboratory notebooks describing these experiments.

7. One crystallization was carried out as follows. Valsartan (2.0 g) was dissolved at reflux in ethyl acetate (15 mL), cooled with slow stirring to 20 °C and after this to 0 °C. The precipitate was separated by filtration and dried at 50°C/10 mm for 1 h to give sample A, with 99.6 % purity by HPLC.

8. Another crystallization was carried out similarly, except using 100 g of valsartan and 1.0 L of ethyl acetate. This was sample B.

9. Samples A and B were provided to my colleague, Dr. Tamás Koltai, for further analysis.

10. The undersigned declares that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the life so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States code and this such willful false statements may jeopardize the validity of the application or any patent issuing thereon.



Valerie Niddam-Hildesheim, Ph.D.  
Project Manager, Process Development Chemistry  
TEVA Pharmaceuticals, Israel

23/07/2008  
Date



~~Exhaustive crystallization~~

Gen. procedure for crystallization:

2 g of VAS-00 was dissolved in the solvent at reflux, then cooled to r.t. with slow stirring and then cooled to 0°C without stirring.

EtOAc - 2 g of VAS-00 from 15 ml of EtOAc

VAS-005-01 - wet

VAS-005-02 - dry (1.0 h at 50°C / 10 mm Hg) HPLC

Toluene - 2 g of VAS-00 from 20 ml of Toluene

VAS-00 was suspended in toluene and heated to reflux at ~~near~~ reflux point melted and gave emulsion with toluene. After cooling VAS-00 was obtained in form of glass-like solid.

VAS-005-03 - wet

VAS-005-04 - dry (1.0 h at 50°C / 10 mm Hg)

$t$ -BuOAc

VAS-005-05 - wet

VAS-005-06 - dry

$\text{MeNO}_2$

VAS-005-07 - wet

VAS-005-08 - dry

$i$ -Pr<sub>2</sub>O - 2 g of VAS-00 from 35 ml of  $i$ -Pr<sub>2</sub>O

VAS-00 was dissolved partially in  $i$ -Pr<sub>2</sub>O at reflux and the most of VAS-00 gave sticky gum residue.  $i$ -Pr<sub>2</sub>O was decanted and the residue was dried at 50°C / 10 mm Hg for 1 h.

VAS-005-09

Exp 169

Jun 16, 03

169



100 g of L-VLS-00 (commercial) were cryst. from 1 L of EtOAc.

VLS-169-01

Trituration of VLS-169-01, L-VLS-00

1)  $H_2O$

a)  $30^{\circ}C$ , 6h VLS-169-02 dry

General: about 4g of L-VLS-00 (cryst. from EtOAc - VLS-169-01) were triturated from diff. solvent (40 ml)

b)  $30^{\circ}C$ , overnight VLS-169-03 dry (-169-06 wet)

c)  $50^{\circ}C$ , 6h VLS-169-04 dry

d)  $50^{\circ}C$ , overnight VLS-169-05 dry (-169-07 wet)

2) Heptane,  $50^{\circ}C$ , 3h VLS-169-08 dry

3)  $n\text{-Pr}_2O$ ,  $50^{\circ}C$ , 3h VLS-169-09 dry

L-VLS-00 was dissolved in MTBE under heating

4)  $H_2O$ ,  $40^{\circ}C$ , overnight VLS-169-10 (wet)

VLS-169-11 (dry)

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## PROFESSIONAL EXPERIENCE

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2008 : Project Manager in Process Development Chemistry, TEVA Pharmaceuticals, Israel  
2000-2008 : Team Leader in Process Development Chemistry, TEVA Pharmaceuticals, Israel.  
1999-2000 : Post-doctoral position : Hebrew University of Jerusalem, Israel.  
1998-1999 : Post-doctoral position, The Weizmann Institute of Science, Rehovot, Israel.

## EDUCATION

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05-06-1997 : Ph.D in Organic Chemistry, University of Aix-Marseille II, France.  
1993-1994 : Post-graduate studies of Organic Chemistry : "Bioactive Compounds : Synthesis and  
1992-1993 : Master of Organic Chemistry bio-organic option, University of Aix-Marseille II, France.

## RESEARCH EXPERIENCE

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2000-2008 : Optimization and parameterization of various processes –process development of new API  
(Active pharmaceutical ingredients).  
1999-2000 : Conception and Synthesis of new inhibitors of MMP-2, catechol derivatives.  
1998-1999 : Temporary sulfur connection as a versatile method in organic synthesis  
1994-1997 : Conception, synthesis and anti-retroviral evaluation of thiophenoxy heterocyclic derivatives.  
April 1993 : Mycoplasmas interest in bacterial and viral infections.  
1993-1994 : Synthesis and fonctionalisation of ureas 1,3-disubstituted for the elaboration of HIV protease  
substrate.

## PUBLICATIONS

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Seven journal articles, in organic chemistry and drug discovery.

Six patent applications on drug discovery, process development, and polymorphism of pharmaceutical compounds; includes seven granted US patents on one granted Canadian patent.